

Meet the Director

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S.
Director

National Institute of Environmental Health
Sciences

National Toxicology Program

Society of Toxicology Annual Meeting
Wednesday, March 9, 2011



National Institute of Environmental Health Sciences

- NOT in Bethesda area
 - Research Triangle Park, NC
- Wide variety of programs supporting our mission of environmental health:
 - National Toxicology Program
 - Intramural laboratories
 - Extramural funding programs
- Funding from 3 Congressional Committees
 - Health – Regular NIH appropriation
 - Interior - Superfund Research Program and Worker Training
 - Energy - Worker Training Program



FY 2008 – FY 2012 Appropriations

Dollars in Thousands

	FY 2008	Stimulus FY 2009	FY09 10	HR 1 FY2010	Request FY2011*	President's FY2012
NIEHS	\$645,669	\$662,820	\$168,057	\$689,781	\$663,646	\$700,537
NIH	\$29,529,524	\$30,317,024	\$10,380,703	\$31,008,788	\$29,379,525	\$31,747,915
Superfund	\$77,546	\$78,074	\$19,297	\$79,212	\$77,546	\$81,085
NIEHS/ DOE Training	\$10,000	\$10,000		\$10,000		

* 2011 Full Year Continuing Appropriations Act passed by the House February 19, 2011.

Congressional Testimony

- Feb 2010 – Senate Subcommittee Superfund, Toxics and Environmental Health. Topic: Exposure Assessment
- Feb 2010 – House Energy and Commerce.
Topic: Endocrine disrupting chemicals in drinking water.
- Mar 2010 – Senate Interior. Topic: Superfund research
- Apr 2010 – House Energy and Commerce, Health.
Topic: HHS role in environment and human health
- May 2010 – Senate Veterans Affairs.
Topic: Dioxin and ischemic heart disease.
- Aug 2010 – Senate Environment and Public Works Subcommittee
Children's Health. Topic: Autism, Neurodevelopmental disorders

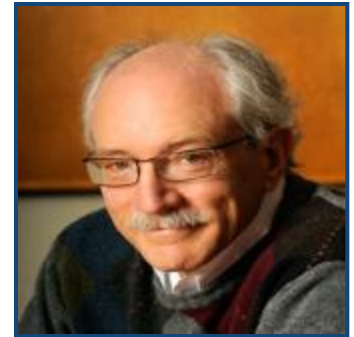
Congressional Testimony

- Sept 2010 – Senate Committee on Veteran’s Affairs. Topic: VA Disability Compensation: Presumptive Disability Decision Making
- Sep 2010 – Senate Breakfast Briefing on Endocrine Disruptors hosted by:
 - Sen. Frank Lautenberg (D-NJ), chairman of the Senate Committee on Environment and Public Works Subcommittee on Superfund, Toxics and Environmental Health
 - Rep. Henry Waxman (D-Calif.), chairman of House Committee on Energy and Commerce
 - Rep. Bobby Rush (D-Ill), chairman of the House Committee on Energy and Commerce Subcommittee on Commerce, Trade and Consumer Protection
 - Rep. Jim Moran (D-Va.), chairman of the House Committee on Appropriations Subcommittee on Interior, Environment and Related Agencies
- Feb 2011 – Senate Committee on Environment and Public Works hearing on Drinking Water Contaminants (especially perchlorate, CrVI and TCE)

Staff Updates:

- **New NIEHS Deputy Director**

Dr. Richard Woychik assumed the role of Deputy Director, NIEHS in January.



- **Permanent Director of the Division of External Research and Training**

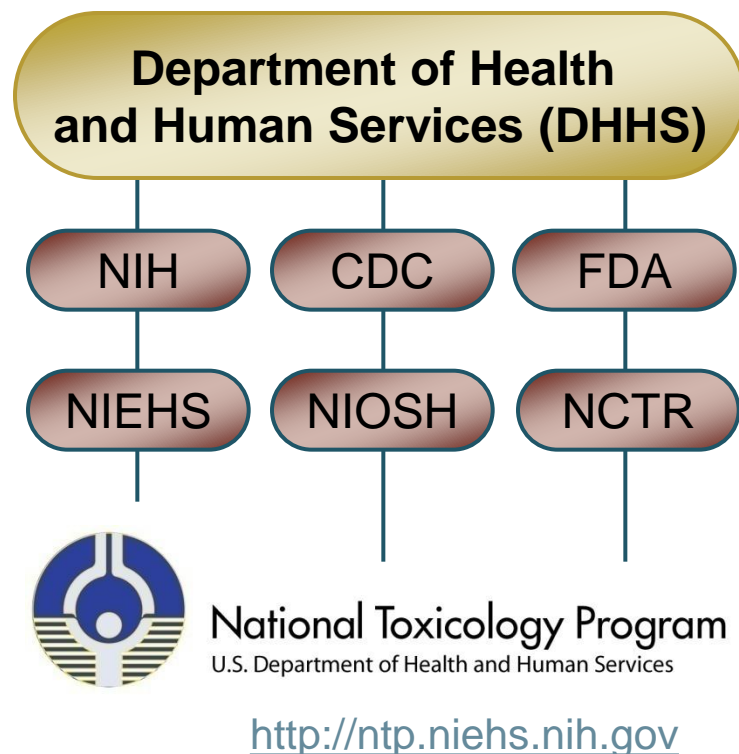
Dr. Gwen Collman was appointed permanent Director of the Division of Extramural Research and Training in December.



- Searches are underway for Scientific Director, Clinical Director, and Associate Director for Management

National Toxicology Program

- Interagency program
 - Established in 1978 to coordinate toxicology research across the Department of Health and Human Services (DHHS)
 - Headquartered at NIEHS
- Research on “nominations”
 - Thousands of agents evaluated in comprehensive toxicology studies
 - Results communicated through technical reports, scientific publications and the web
- Analysis activities
 - Report on Carcinogens (RoC)
 - Center for the Evaluation of Risks to Human Reproduction (CERHR)
 - NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM)

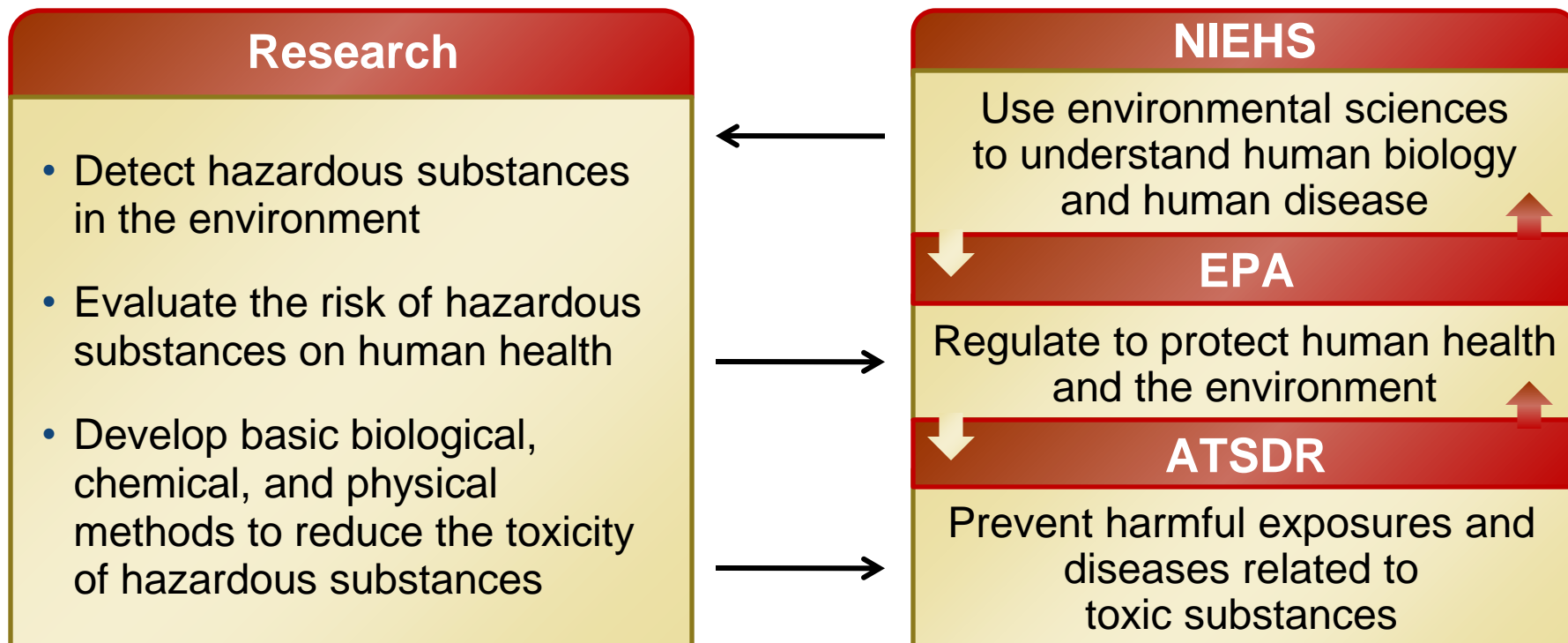


New and Renewed Areas of Emphasis for NTP

- Better coordination across the Federal government
- Develop new methods for efficient, thorough toxicological assessments
- Increase understanding of exposure-response relationships and issues of dosimetry
- Integrate results from new “data rich” techniques (i.e. genomics, high through-put screening) with traditional toxicology data to provide public health context
- Toxicity for the 21st Century or “Tox21”
 - MOU between NTP, EPA and NHGRI
 - High throughput, robotic testing of toxic compounds in cell and molecular assays
 - Using knowledge of biological response to identify toxicity pathways
 - Prioritization for further testing



Superfund Research and Worker Training Program



NIEHS Worker Education and Training Program Makes Awards for 2010-2011

- **Hazardous Waste Worker Training Program** – \$20.6 million to 20 organizations
- **Nuclear Weapons Cleanup Training Program** – \$9.6 million to eight organizations
- **Minority Worker Training Program** – \$3.5 million to four organizations
- **Hazmat Disaster Preparedness Training Program** – \$2.3 million to 10 organizations



Institute Oil Spill Work Continues

- **Worker Education and Training** – safety training for 140,000 oil spill clean up workers
- **Toxicology Research** – NTP studies on oil and dispersants
- **Research Consortia Funding**– grants for researcher-community partnerships
- **NIEHS Grants** – research on the health effects of oil spill on gulf communities and special populations
- **NIH GuLF STUDY** – research on the long-term health effects of the oil spill on clean up workers.

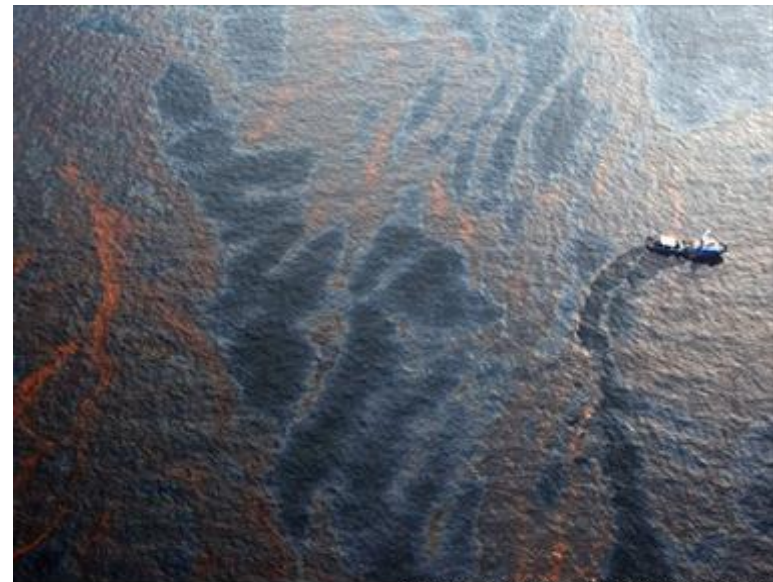


PHOTO: CHRIS GRAYTHEN/GETTY IMAGES

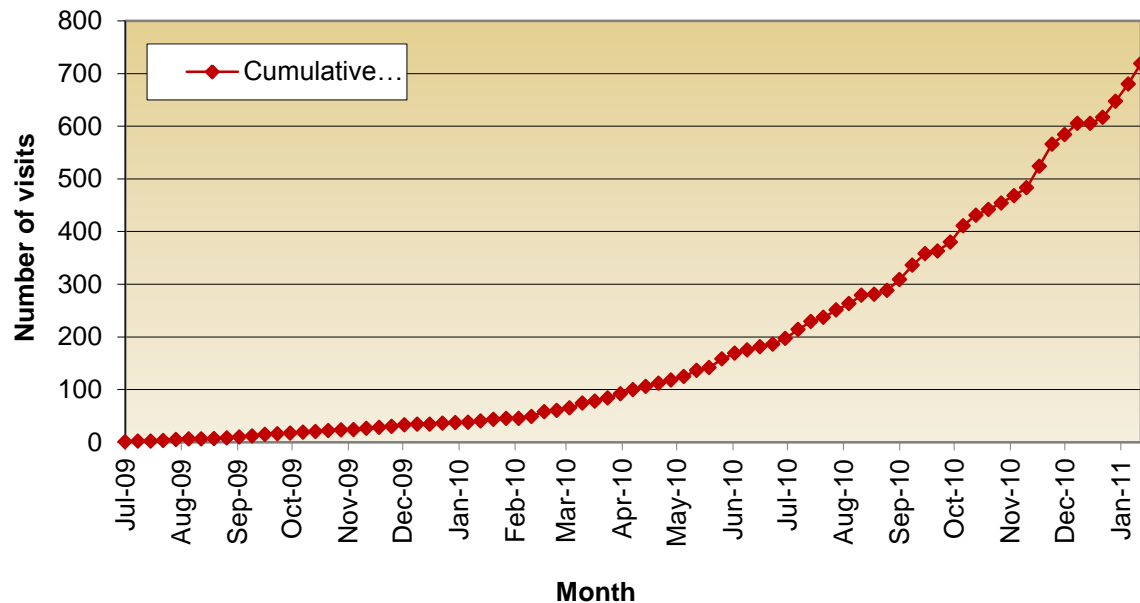
<http://www.niehs.nih.gov/about/od/programs/gulfspill/index.cfm>

Congressional Testimony on Oil Spill

- **June 15, 2010:** Senate Committee on Health, Education, Labor, and Pensions
 - HHS actions to identify and address health effects of the BP Oil Spill
- **June 16, 2010:** House Subcommittee on Health, Committee on Energy and Commerce – June 16, 2010
 - Evaluating the Health Impacts of the Gulf of Mexico Oil Spill
- **Sept 15, 2010:** House Committee on Transportation and Infrastructure
 - Enbridge Pipeline Oil Spill in Marshall, Michigan

NIEHS Clinical Research Unit

Cumulative CRU Visits



Tissue Type	Research Description
punch biopsy of skin	generation of inducible pluripotent stemm cells from skin fibroblasts
blood cells	response of inflammatory cells to oxidative injury
alveolar macrophages	modulators of mRNA stability in the regulation of innate immunity
serum	BPA biomonitoring study in cashiers
serum, blood cells	glucocorticoid receptor SNP effects of steroid responsiveness (EPR and other)
serum	role of NAG-1 in inflammatory bowel disease
blood cells	oxidative injury markers
serum	Gene/environment factors in the pathogenesis of autoimmune myositis (satellite site)
blood cells	calcium channel effects on immune cell function
blood cells, alveolar macrophages	p53-inducible innate immune genes (EPR and other)
blood cells	Role of eicosanoids in T cell function in asthma

Institute Workshops, Meetings, Conferences

- Expert Panel Workshop to Examine the Role of the Environment in the Development of Autoimmune Disease
- Inaugural meeting of the Interagency Breast Cancer and Environmental Research Coordinating Committee (IBCERCC)
- Global Alliance for Clean Cookstoves Launch
- Health Consequences from Xenobiotic – Gut Microbiome–Host Interactions



Institute Workshops, Meetings, Conferences

- Autism and the Environment: New Ideas for Advancing the Science
- Worker Education and Training Fall Awardee and Technical Meeting
- NIEHS Centers for Nanotechnology Health Implications Research (NCNHIR) Consortium Meeting
- DISCOVER: Translation and Beyond
- NIEHS Workshop on Air Pollution and Brain Health



Institute NTP Meetings and Workshops

ICCVAM Workshops on Best Practices for Regulatory Safety Testing:

- Assessing the Potential for Chemically
Induced Eye Injuries
 - January 19, 2011
- Chemically Induced Allergic Contact Dermatitis
 - January 20, 2011



NTP Workshop: Role of Environmental Chemicals in the Development of Diabetes and Obesity

January 11-13, 2011

- Brought together experts on diseases, toxicology, epidemiology and HTS/bioinformatics
- Identified toxicity pathways (AhR, PPAR, CAR, PXR, others) associated with diabetes and obesity in studies of arsenic, phthalates, organotins, nicotine, etc
- Identified disease pathways (insulin signaling, adipocyte differentiation, feeding behavior etc.) associated with diabetes and obesity
- Identified some critical future HTS targets to better understand associations between environmental exposures and these diseases.



NTP Workshop:
Role of Environmental Chemicals
in the Development of Diabetes
and Obesity

January 11-13, 2011
Raleigh Marriott Crabtree Valley • 4500 Marriott Drive

There has been increasing interest in the concept that environmental chemicals may be contributing factors to the epidemics of diabetes and obesity. The National Toxicology Program (NTP) is holding a workshop to evaluate the science associating exposure to certain chemicals or chemical classes with the development of diabetes and obesity in humans. Participants at the workshop will:

- Evaluate strength/weaknesses, consistency, and biological plausibility of findings reported in humans and experimental animals for certain environmental chemicals including arsenic and cadmium, PCBs, DDT/DDE, other organohalogenes, bisphenol A, phthalates, and organotins
- Identify the most useful and relevant endpoints in experimental animals and in vitro models
- Identify relevant pathways and biological targets for assays for the Toxicology Testing in the 21st Century high throughput screening initiative ("Tox21")
- Identify data gaps and areas for future evaluation/research

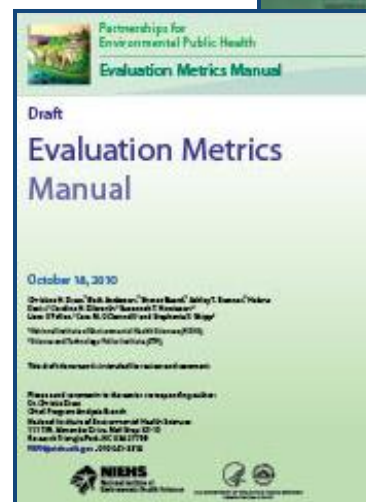
The format of the workshop includes both plenary talks and breakout groups. The workshop is open to the public with time set aside in the agenda for public comments during the plenary session on the first day. The public can attend the breakout groups as observers. A literature review document will be prepared prior to the meeting. Information about the workshop and on-line registration are available from the NTP website. Registration is on a first come basis and is limited to 100 people. For additional information, contact Dr. Kristina Thayer (thayer@niehs.nih.gov or 919-541-5021).

This workshop is sponsored by the National Institute of Environmental Health Sciences/NTP, U.S. Environmental Protection Agency, and the FDA National Center for Toxicological Research.



Institute Highlights – Translation

- Superfund Film:
“In Small Doses: Arsenic”
- Climate Change and Human Health white paper is basis for research agenda
- PEPH Metrics Manual Launched for Comment – can be downloaded from PEPH website under Materials



Recent Science Advances

- Environmental Alterations to Genetic Networks
 - Rewiring of genetic networks in response to DNA damage.
Bandyopadhyay et al., Science. 2010 Dec 3;330(6009):1385-9
- Epigenetic Silencing in Lung Cancer
 - Re-expression of CXCL14, a common target for epigenetic silencing in lung cancer, induces tumor necrosis.
Tessema et al., Oncogene. 2010 Sep 16;29(37):5159-70
- Mitochondrial Dysfunction in Autism
 - Mitochondrial dysfunction in autism.
Giulivi et al., JAMA. 2010 Dec 1;304(21):2389-2396.



Recent Science Advances

- Profiling DNA Methylation and Identification of Monoallelic Epigenetic Modifications
 - Comparison of sequencing-based methods to profile DNA methylation and identification of monoallelic epigenetic modifications.
Harris et al., Nat Biotechnol. 2010 Oct;28(10):1097-1105.
- New Exposure Paradigm
 - Environment and disease risks.
Rappaport S, Smith MT. Science. 2010 Oct 22;330(6003):460-461
- Mechanistic Basis of Resistance to PCBs in Atlantic Tomcod from the Hudson River
 - Isaac Wirgin, Nirmal K. Roy, Matthew Loftus, R. Christopher Chambers, Diana G. Franks, and Mark E. Hahn.
Published Online 17 Feb 2011
Science DOI: 10.1126/science.1197296



Atlantic Tomcod from Hudson River
Photo by Mark Mattson of Normandeau Associates, Inc.

NIH Roadmap - Epigenomics of Human Health & Disease

- **Goal: to investigate the role of epigenetic changes in a wide range of human diseases**
 - 23 grants funded by different NIH institutes and centers
 - Variety of diseases and conditions, including Alzheimer's, pregnancy outcomes, mental health disorders, asthma, lupus, atherosclerosis and hypertension
- **NIEHS-funded grants:**
 - Investigating prenatal exposures and epigenetic changes in development of autism (Fallin and Feinberg)
 - Exposure to BPA and the development of breast cancer (Huang)
- **Recent re-release of RFA-ES-10-002 currently under review**



NIH Genes, Environment and Health Initiative Exposure Biology Program

Nearing Completion

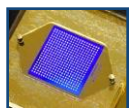


- **'Prototypes' in hand for ALL funded projects including:**

- 8 'Wearable' sensors for measuring airborne chemical exposures
- 7 Tools for assessing diet and/or physical activity
- 5 Tools for measuring psychosocial stress and the use of addictive substances
- 8 Candidate biomarker panels for assessing the biological response to environmental stressors
- 5 Technologies for measuring biomarkers in biological samples

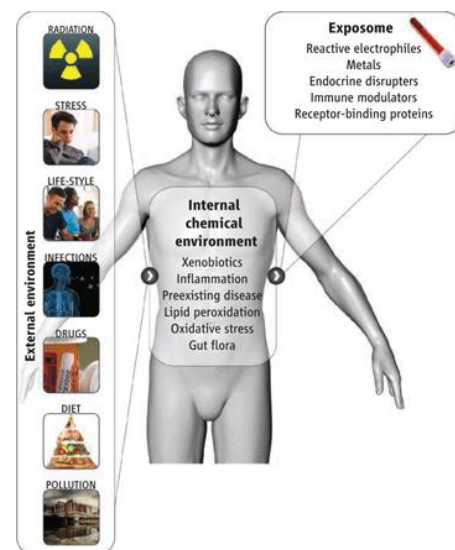
- **Notable Successes:**

- Testing of prototype chemical sensors in the CDC-HUD Green Housing Study, the National Children's Study and the UK Biobank
- Use of the 'comet chip' in measuring response to arsenic in Thailand
- Numerous commentaries, editorials and news pieces on Exposure Biology



- **Open Grantee Meeting:**

- April 14, 2011 at NIEHS, details on our home page



EVERY BITE YOU TAKE

If a camera snaps everything you eat, you can't lie about it later. That's why scientists are building high-tech gadgets to measure the human 'exposome'.

BY BRENDAN BORRELL



NIH Genes, Environment and Health Initiative Exposure Biology Program

Future Activities

- **Released solicitations:**
 - Validation of the Prototypes (RFAs in review now)
 - Development of methods for GxE integration (PAR applications received)
 - Supplements on methods for Phenotyping (PhENX)
- **Programs being considered:**
 - Proof of Principle Studies
 - Adding genomic info to “E” studies
 - Adding new environmental measures to “G” studies
 - Secondary analysis of existing GWAS data
 - Functional analyses of candidate GxE interactions
 - Field-deployable tools for biomonitoring of environmental exposures
 - Coordination of existing efforts around a focused exposure

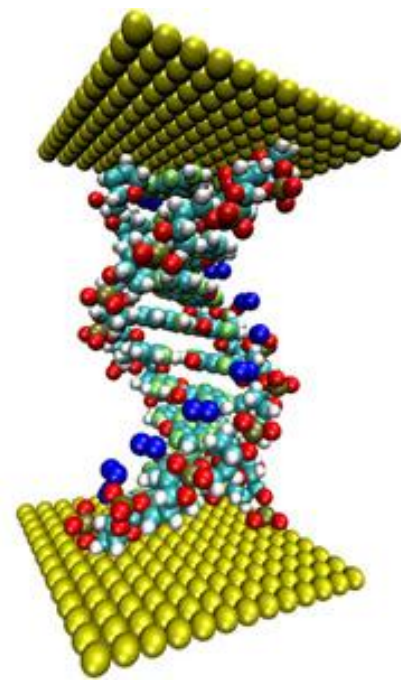
BPA Research

- NIEHS funds 39 grantees (12 ARRA)
- Developed working consortium
 - Integration and collaboration among projects and endpoints
 - Listserv
 - Yearly grantee meetings
 - Working groups via teleconference quarterly (obesity, neurobehavioral, cancer, reproductive, pharmacokinetics, low dose, gene expression)
 - Sharepoint site lists all publications/abstracts
 - Contract to assess success of this unique approach to integrate research and researchers across a focused area
- Developing consortium of grantees to add disease focused endpoints to an NTP/FDA guideline study of BPA toxicity

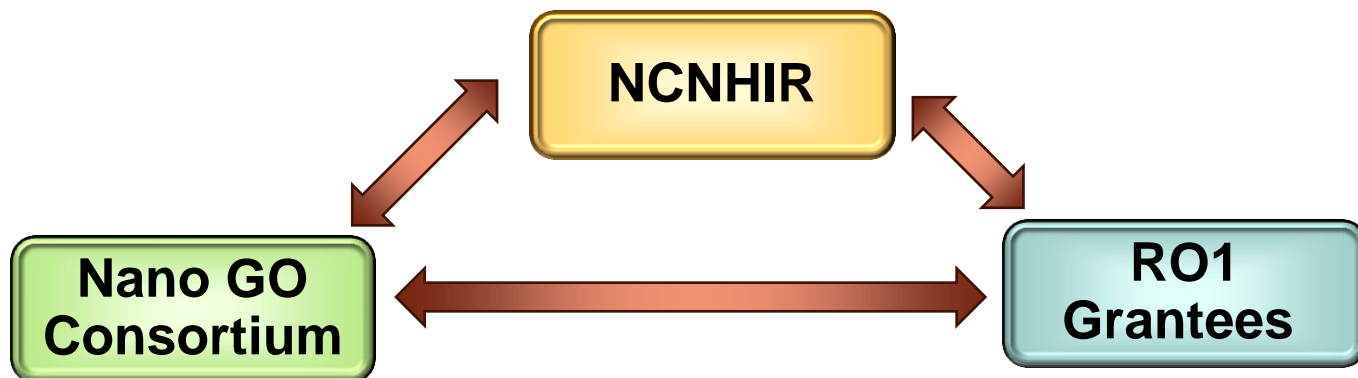


Nanotechnology Environmental Health & Safety Research Strategy

- Develop/identify relevant *in vitro* and *in vivo* assays to predict biological/toxicity responses
 - Nano Grand Opportunity Consortium (ARRA funds)
- Gain fundamental understanding on interaction of ENMs with biological systems as governed by their physical and chemical properties
- Utilize this knowledge to develop models (QSAR/PBPK) ENM health effects
 - NIEHS Centers for Nanotechnology Health Implications Research (NCNHIR) formed in 2010 through U19/UO1 mechanism
- Methods to quantify exposure to ENM in diverse matrices



NIEHS Centers for Nanotechnology Health Implications Research Consortium



- Utilize diverse expertise from the leaders in the field to work together in addressing key issues using common library of ENMs
- Investigate in multiple systems to gain comprehensive understanding
 - Cellular, molecular, ADME, tissue/organ-specific findings
- Assess and integrate salient features from diverse Risk Assessment frameworks to develop and validate robust model(s).

Environmental Health Research: Planning for the Future


The Challenge

- How do we come together to think strategically about the breadth, scope, participants, and goals for Environmental Health Research, a multi-science discipline primed for significant impact on human health in the 21st Century?
- How do we create an Environmental Health Research Strategy that provides the data and information needed by the multiple audiences who use EHS data?
- Do we have the right tools and methods to do Environmental Health Research in the 21st Century?
- How can we integrate better new methods and technologies into science policy?



NIEHS Visionary Ideas Website





NIEHS
National Institute of Environmental Health Sciences – National Institutes of Health




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Visionary Ideas

[Strategic Plan](#)

How does it work?

-  Users submit their ideas.
-  Our community discusses and votes for ideas.
-  The best ideas bubble up to the top.

Welcome to the National Institute of Environmental Health Sciences (NIEHS) Visionary Ideas for Strategic Planning

Visionary Ideas are thoughts you have regarding the mission, purpose, direction, goals, leadership, responsibilities, and general reason for being of the NIEHS. Here, you can submit, vote on, or comment on Visionary Ideas, as well as discuss strengths, weaknesses, opportunities, and threats for NIEHS. We invite you to step back, take a broad view, and think big! You will be asked to register so that you can come back later and check out what's happening on the site.

[To submit an idea](#), click the button below.
[To vote on an idea](#), click the up or down thumb to the left of the idea.
[To comment on an existing idea](#), click in the box below it.
[To tag an idea or comment](#), click the Add Tag link.
[To see all ideas associated with a specific tag](#), click that tag in the What We're Discussing box.
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[I agree](#)

2
votes



[I disagree](#)

[Add your comment](#)


Submitted by contactus 1 day ago

Public Health Means Prevention

My idea is that as a public health institute, NIEHS should consider prevention as the cornerstone and primary motivation of all of its activities ...more »


[I agree](#)

1
vote



[I disagree](#)

[1 comment](#)


Submitted by contactus 1 day ago

Environmental Health and Medicine

NIEHS should put efforts into better integrating traditional environmental health fields and disciplines, as well as research approaches, with ...more »


[I agree](#)

1
vote


[I disagree](#)

Public Health

Prevention is important, but the bigger topic is Public Health. NIEHS should steer itself explicitly toward the improvement of public health. ...more »

<http://strategicplan.niehs.nih.gov>



NIEHS/NTP PROVIDING **LIVE** **UPDATES**

at the Society of Toxicology
Annual Meeting in Washington, D.C.
March 6-10, 2011



JOIN US AT:
www.niehs.nih.gov/liveatsot



OR FOLLOW ALONG ON TWITTER:
www.twitter.com/niehs



BENCHMARKS in TOXICOLOGY



Paracelsus Paracelsus, a 16th-century physician, demonstrated an understanding of the dose-response relationship by saying, "All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy." Because of this, he is often referred to as the "father of toxicology."

Bernardino Ramazzini The father of occupational medicine, Ramazzini issued concerns about workplace exposure to chemical hazards, including heavy metals. His book *Diseases of Workers*, first published in 1700, is the first comprehensive work on occupational diseases.

Sir Percival Pott In 1775, Pott, an English surgeon, became the first to describe an occupational cancer by linking scrotal cancer in chimney sweeps to soot exposure.

Rachel Carson In her 1962 book *Silent Spring*, Carson documented the detrimental effects of DDT (dichlorodiphenyltrichloroethane). She led the crusade against the use of the pesticide, which was eventually banned in 1972. Her work is credited with advancing the environmental movement and raising public awareness of environmental concerns.

Louis Casarett and John Doull Casarett and Doull are the first editors of the textbook *Toxicology: The Basic Science of Poisons* (1975). Now in its seventh edition, the classic has been instrumental in training scientists for more than 35 years.

Frances Kelsey During the late 1950s and early 1960s, in response outside the United States, use of thalidomide to relieve morning sickness in pregnant women tragically resulted in thousands of babies born with limb deformities. Because of Kelsey's efforts at the U.S. Food and Drug Administration (FDA), the drug was never approved for use in the United States, thus avertting a health disaster of greater proportions.



Irving Selikoff and J. Christopher Wagner Selikoff's groundbreaking studies of asbestos workers in the 1960s and Wagner's experimental approach to asbestos toxicology firmly established the connection between asbestos and lung disease. Their work provided the scientific basis for the regulation of asbestos.

People Contributors to the field of toxicology



1906 Pure Food and Drug Act One of the first laws regulating the marketing of drugs was the 1906 Pure Food and Drug Act, which required accurate labeling of dosage and contents. Prior to this, many drugs listed unsubstantiated benefits from secret ingredients. Though the law has been largely replaced by the Federal Food, Drug, and Cosmetic Act, it did serve as the driving force for the eventual creation of the FDA.

1938 Federal Food, Drug, and Cosmetic Act (FDCA) In 1937, more than 100 people died from sulfanilamide medicine mixed with deadly diethylene glycol. This disaster led to the passage of the FDCA, which required companies to perform safety testing and obtain FDA approval prior to marketing new drugs. The 1938 Food Additives Amendment, also called the Delaney Clause, prohibits the approval of any food additive shown to induce cancer in humans or animals.

1947 Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) FIFRA provided for federal regulation of pesticide distribution, sale, and use to protect human health and prevent unreasonable adverse effects on the environment.



1960s and 1970s Federal agencies established Increased public concern over the environment, health, and safety prompted the establishment of several key agencies. Today the U.S. government employs the largest number of toxicologists worldwide, at places such as the National Institute of Environmental Health Sciences (NIEHS), the U.S. Environmental Protection Agency (EPA), the Occupational Safety and Health Administration, and the National Institute for Occupational Safety and Health.

1970s Lead reduction efforts Through the Clean Air Act, the federal ban on lead-containing paint, and other efforts, the United States has seen a dramatic decline in average blood lead levels. Lead emissions in the United States have been reduced significantly since the 1970s.

1976 Toxic Substances Control Act (TSCA) Under TSCA, the EPA regulates many existing chemicals and the introduction of new ones. TSCA addresses the production, importation, use, and disposal of specific chemicals, including polychlorinated biphenyls (PCBs), asbestos, and lead-based paint.

1978 National Toxicology Program (NTP) Recognizing that many human diseases were thought to be directly or indirectly related to chemical exposures, the NTP was established in 1978 to coordinate federal government toxicology testing, strengthen the science base in toxicology, develop and validate improved testing methods, and inform agencies, scientific and medical communities, and the public about potentially toxic chemicals.

1978 Good laboratory practices (GLP) GLP principles were established to promote the quality and validity of test data used for determining the safety of a variety of regulated products for regulatory authorities. GLP promotes confidence that data from laboratory studies can be relied upon when conducting risk assessments.

1980 Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) The crisis in New York's Love Canal neighborhood brought focus to the issue of toxic industrial waste. This and other high profile hazardous substance cases prompted Congress to pass CERCLA, more commonly known as Superfund, to provide broad authority and funds to clean up hazardous waste sites.

2008 Toxicology testing in the 21st century (Tox21) Together, the NIEHS, NTP, EPA, FDA, and National Human Genome Research Institute are advancing the state of toxicity testing using high throughput screening methods enabled by advances in computing, robotics, and cell-based analytical approaches, in addition to testing thousands of chemicals and mixtures. The collaboration seeks to identify new mechanisms of chemical activity in cells to better predict human response to toxic substances.



Federal Government Efforts Protecting the nation's health



1971 Methylmercury poisoning in Iraq Seed grain coated with methylmercury fungicide was imported into Iraq and mistakenly consumed as food, killing hundreds. Studies of the tragedy provided toxicologists in regulatory agencies with one of the first opportunities to apply human data in establishing safe levels of exposure to a chemical.

1970s Popularization of risk assessment A methodology for predicting the incidence of human cancers based on animal data offered quantitative estimates of risk for a given chemical dose. This model was quickly used to prioritize the regulation of dozens of substances found to be carcinogenic.

1983 The Red Book The National Research Council's *Risk Assessment in the Federal Government: Managing the Process* outlines principles for conducting risk assessments. This guide (and others) provides enduring concepts in toxicology-based approaches that continue to drive decision making in industry, academia, and government.

1980s Paradigm shift The mid-1980s brought a change in toxicologic thinking from hazard and risk assessments based on typical end points in animal studies, toward a mechanism-driven integrated approach, including *in vitro* studies and modeling approaches.

1980s PBPK modeling Used in research and development and health risk assessment, physiologically based pharmacokinetic (PBPK) mathematical models describe the uptake, distribution, metabolism, and elimination of chemicals in the body and are used to predict the toxicity of a chemical in humans on the basis of animal data. In 1989, EPA used PBPK data to revise its inhalation risk assessment for the solvent trichloroethylene.

1980s Weight of evidence Beginning with their assessment of color additives, officials at FDA widened use of the weight of evidence approach to evaluate the findings of a body of studies versus a positive, statistically significant result from a single study.

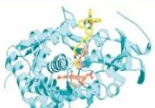
1986 Health risk assessment of lead EPA established a certain blood lead level as a level of concern for adverse health effects to children's neurobehavioral development. This assessment was at the forefront of major changes in public health policies, including removal of lead from gasoline.



1990s Threshold of toxicological concern (TTC) TTC is a human exposure threshold value set for chemicals below which there would be no appreciable risk to human health. TTC has become a valuable risk assessment tool for substances present in products in very low amounts, even where toxicity data may be lacking.

2008 Bovine corneal opacity and permeability (BCOP) assay In an effort to minimize harm to animals used in research, members of the federal Interagency Coordinating Committee on the Validation of Alternative Methods recommended approval for use of the BCOP assay as an *in vitro* test for detecting eye irritants.

Risk Assessment Using toxicology to reduce harm



1955 Discovery of cytochrome P450 enzymes (CYPs) The discovery of CYPs helps to understand how chemicals are transformed in the body into active compounds. CYPs in humans are present throughout the body and play an important role in drug metabolism, bioactivation, and excretion.

1960s Aerosol science Key insights into the physical and chemical properties of small particles in gases helped reveal how adverse health effects occur in humans. These contributions in inhalation toxicology continue to have a great impact on our understanding of air pollutants.

1960s Toxic solvents Numerous studies, including research focusing on worker exposure, expanded our understanding of the toxicity and metabolism of industrial solvents.

1971 Role of electrophilic intermediates Electrophilic intermediates were identified as key contributors in the conversion of chemicals into active agents. This opened the door to understanding the metabolic activation of toxicants, carcinogens, and pharmaceuticals.

1970s Formaldehyde Research on formaldehyde, a chemical used in a variety of materials from consumer products to disinfectants, revealed complicated mechanisms of toxicity.

1970s Ames test This simple screening assay examines bacterial mutation to determine whether a chemical damages DNA and might cause cancer, and today is still one of the most utilized tests to screen chemicals and drugs before approval is received for marketing. The Ames test has broad application in pharmaceuticals, pesticides, industrial chemicals, and environmental sample testing, and it has reduced animal use in testing.



1976 Aryl hydrocarbon receptor (AHR) The cellular environmental sensor AHR mediates the expression of genes involved in the metabolism and detoxification of environmental pollutants such as dioxins and polychlorinated biphenyls. The discovery was critical to the understanding of toxicology at the molecular level.

1980s Alpha 2u globulin nephropathy In male rat-specific disease of the kidney increases the incidence of renal cancer. Research has demonstrated that the biochemical processes for the disease in male rats cannot occur in humans. This finding has implications for risk assessment and regulation, which generally assumes that chemicals producing tumors in animals are potentially hazardous to humans.

1980s Nongenotoxic carcinogens Pioneering research illustrates the ability of carcinogens to act through genotoxic (altering genetic material of cells) and nongenotoxic mechanisms. This led to the discovery of several mechanisms that cause DNA damage or increased cell proliferation.

1990s Omics Toxicogenomics is a field combining toxicology with genomics research and other omics technologies, together with groundbreaking advances in analytical and computational capabilities, improve our understanding of the pathways leading to toxicologic effects.

Mechanisms & Metabolism Improving our understanding of biological processes

Thank you!



National Toxicology Program
U.S. Department of Health and Human Services

